

EDITORIAL COMMENT

Platelet Function Measurement in Elective Percutaneous Coronary Intervention Patients

Exploring the Concept of a P2Y₁₂ Inhibitor Therapeutic Window*

Udaya S. Tantry, PhD,[†] Young-Hoon Jeong, MD, PhD,[†]
Eliano P. Navarese, MD,[‡] Paul A. Gurbel, MD[†]

Baltimore, Maryland; and Cotignola, Ravenna, Italy

When clopidogrel was first clinically used, the relation between the pharmacodynamic effect and thrombotic event occurrence was unknown. Moreover, when the new P2Y₁₂ inhibitors were developed, the desired level of on-treatment platelet reactivity to adenosine diphosphate to avoid ischemic event occurrence was highly debated and some recommended that near-100% inhibition should be the target. Concern surrounding the clinical implications of aggregometry-defined poor platelet inhibition in clopidogrel-treated elective percutaneous coronary intervention (PCI) patients arose over 1 decade ago (1). In that study, approximately 30% had a $\leq 10\%$ decrease in aggregation at 24 h after a 300-mg load; these patients were defined as resistant. It was suggested that, “further study is necessary to investigate the mechanisms of these findings and how they correlate with the occurrence of ischemic events” (1).

See page 281

Aggregometry-defined clopidogrel nonresponsiveness was first studied in relation to post-PCI ischemic event occurrence in ST-segment elevation myocardial infarction

patients (2). On-treatment reactivity was subsequently suggested as a better ischemic risk predictor than nonresponsiveness, because risk was potentially overestimated in patients with low pre-treatment platelet reactivity and underestimated in patients with high pre-treatment platelet reactivity (3).

How far have we come since 2004? Numerous studies conducted globally in thousands of patients have measured the intensity of the platelet response to adenosine diphosphate, reaching the identical conclusion: patients with high on-treatment platelet reactivity (HPR), determined either immediately before PCI or at the time of hospital discharge, are at increased risk for short- and long-term ischemic event occurrence (4). Platelet reactivity cutoff values have been reported in a white paper for consideration in future personalized antiplatelet therapy studies (4). Platelet function testing in PCI patients is now addressed in American and European treatment guidelines (5,6). Early small turbidimetric aggregometry-based studies demonstrated that short- and long-term ischemic event occurrences, including periprocedural myocardial infarction (MI) and stent thrombosis (ST), were not linearly related to on-treatment platelet reactivity but instead occurred above a moderate level of platelet reactivity (7). On the basis of this preliminary evidence, the concept of a “therapeutic window” of platelet reactivity similar to the international normalized ratio range used for Coumadin therapy was first hypothesized (7). The availability of this information in the early 2000s might have limited the speculation about the desired target for platelet reactivity during new P2Y₁₂ inhibitors therapy.

Since approximately 2005, an explosion of translational research using the VerifyNow P2Y₁₂ assay (Accumetrics, San Diego, California), a turbidimetric-based assay that measures the agglutination of platelets to fibrinogen-coated beads, has occurred. This work was facilitated by the user-friendliness of VerifyNow P2Y₁₂ assay—a technique that requires no pipetting, no centrifugation, and minimal labor—allowing for enrollment of increasingly larger numbers of patients. However, the essential message from the much-larger VerifyNow P2Y₁₂ assay-based studies seems essentially the same as the one from conventional aggregometry-based studies (4).

A potential therapeutic window was first demonstrated with impedance aggregometry (8). In this issue of *JACC: Cardiovascular Interventions*, Mangiacapra et al. (9) further explored the “therapeutic window” concept with VerifyNow P2Y₁₂ assay in 732 aspirin-treated elective PCI patients either loaded with 600-mg clopidogrel or receiving a 75 mg/day maintenance dose for ≥ 5 days. The authors of the current study should be acknowledged for their many contributions to the field of personalized antiplatelet therapy. Platelet function was measured before PCI—as in other European studies where pre-treatment is common—allowing the opportunity to study the relation of periproce-

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [†]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, Maryland; and the [‡]Interventional Cardio-Angiology Unit, GVM Care and Research, Cotignola, Ravenna, Italy. Dr. Tantry has received honoraria from Bayer and Accumetrics. Dr. Jeong has received honoraria for lectures from Sanofi-Aventis, Daiichi Sankyo, Inc., and Otsuka. Dr. Navarese has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Gurbel has received research grants, honoraria, and consultant fees from AstraZeneca, Merck, Medtronic, Eli Lilly/Daiichi Sankyo, Inc., Sanofi-Aventis/Bristol-Myers Squibb, Portola/Novartis, Boston Scientific, Bayer, Accumetrics, Boehringer Ingelheim, and Johnson & Johnson.

dural events (MI and bleeding) to on-treatment reactivity. The 30-day net adverse event rate (occurrence of ischemic events [death, MI defined as creatine kinase-myocardial band $>3\times$ upper limit of normal, revascularization] or bleeding [Thrombolysis In Myocardial Infarction major bleeding or large entry-site (>10 cm) hematoma]) was 12.3% and is similar to the frequency reported in other studies by the same authors where periprocedural MIs and bleeding events were captured (10–12). In addition, the receiver-operating characteristic (ROC) curve-defined cutpoints for ischemic events and bleeding were very similar to the current study.

Importantly, in the current study, approximately 70% of the ischemic events were periprocedural MIs, and approximately 80% of bleeding events were entry site hematomas. The ROC curve-defined cutpoint for ischemic events was ≥ 239 P2Y₁₂ reaction units (PRU) (sensitivity 63%, specificity 70%) and for bleeding was ≤ 178 PRU (sensitivity 78%, specificity 63%). A patient-based meta-analysis ($n = 3,059$) of studies employing VerifyNow P2Y₁₂ assay in PCI patients lends further support to the clinical utility of platelet function testing; patients with ≥ 230 PRU had twice the ischemic event rate (13). Most recently, in the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) registry that enrolled even more patients ($n = 8,575$), a ≥ 230 PRU was attributable to 40% of 30-day probable or definite ST occurrence, and when HPR was defined as PRU >208 , the level of attribution increased to approximately 50% (14).

On the basis of ROC curve analysis, Mangiacapra et al. (9) proposed a therapeutic window with specific thresholds (PRU = 179 to 238) to define a group at lower risk for both 30-day ischemic and bleeding events. A central question is whether ROC curve analysis is the optimal method to determine a potential therapeutic window for personalized antiplatelet therapy. The largest prospective randomized personalized antiplatelet study, GRAVITAS (Gauging Responsiveness with A VerifyNow P2Y₁₂ assay-Impact on Thrombosis And Safety), where periprocedural events were not captured, failed to demonstrate the clinical usefulness of personalizing antiplatelet therapy on the basis of a ≥ 230 -PRU ischemic cutoff (15). In a subanalysis of GRAVITAS in patients treated with standard-dose clopidogrel, a lower ischemic cutpoint—approximately 170 PRU—was associated with optimal identification of patients destined to experience 6-month ischemic event occurrence; patients with a PRU <170 were ischemic event-free—in these patients the sensitivity of the test was 100% (15).

Among ischemic events, ST is the most catastrophic. Therefore, it could be suggested that the ischemic “cutoff” should be based not on an ROC curve analysis but on a cutoff with very high sensitivity to guarantee immunity or near immunity to this event. In the current study, all 4 patients with 30-day ST had PRU >239 . On the basis of the much larger ADAPT-DES registry, the prevalence of

ST was approximately 0.24% in the lowest 2 quintiles (PRU <160), compared with 0.78% in the upper 2 quintiles (PRU >217) (14). Importantly, approximately 50% of the ADAPT-DES patients presented with acute coronary syndromes, whereas the current study enrolled only stable patients. Therefore, the optimal ischemic cutoff might be higher in the lower-risk patient group studied by Mangiacapra et al. (9). The cutpoint for periprocedural MI and ST might also differ, because the underlying mechanisms are not entirely shared.

An alteration in antiplatelet therapy intended to increase platelet reactivity in a patient deemed “at risk” for bleeding on the basis of ROC curve analysis might have a dire clinical consequence: the occurrence of ST. Approximately one-half of the ischemic events in the current study occurred in patients with PRU below the proposed ischemic cutoff, and approximately 25% of bleeding events occurred in patients with a PRU above the bleeding cutoff (9). This significant event occurrence rate within the proposed window poses a challenge for its clinical utility.

In the current study most of the bleeding events were vascular access site-related (9). These events might not be “platelet-centric” in mechanism but rather influenced by multiple factors, including arterial access, local techniques to achieve hemostasis, vessel wall characteristics, and concomitant medications. Thus, the current bleeding cutoff might have been driven upward in an ROC curve analysis by vascular site-related bleeding events unrelated to platelet reactivity. Large entry site hematoma frequency might be reduced by radial access (used in only approximately 4% in the current study). A lower PRU in the setting of radial access might ensure greater protection against the occurrence of the catastrophic event, ST, but at the same time lessen bleeding risk. Unlike the data for ST, a highly “platelet-centric” event, the data available linking platelet function to bleeding are much less robust. Others have suggested a PRU bleeding threshold much lower than Mangiacapra et al. and Campo et al. (9,16). The authors also proposed to treat patients with HPR with more potent P2Y₁₂ blockers (9). However, most patients treated with either prasugrel or ticagrelor will have on-treatment PRU <180 , thus falling outside their suggested therapeutic window (17,18).

At this time, the evidence is strong for a link between on-treatment platelet reactivity and ischemic event occurrence, particularly ST. The level of platelet reactivity where risk increases is likely influenced by the acuity of the disease and might explain some of the differences in reported ischemic thresholds. However, the evidence for a bleeding threshold seems more tenuous and is likely related to the heterogeneous underlying mechanism. As the authors correctly concluded, larger studies are needed to validate the concept of a therapeutic window for P2Y₁₂ inhibitor therapy. Certainly, an important message of this investigation and

many others that preceded it is that ischemic events are not further avoided by achieving very low levels of on-treatment reactivity. However, very low reactivity is commonly observed during therapy with new P2Y₁₂ inhibitors, raising the issue of unnecessary enhancement of bleeding risk in these patients (17,18).

Reprint requests and correspondence: Dr. Paul A. Gurbel, Sinai Center for Thrombosis Research, Cardiac Catheterization Laboratory, 2401 West Belvedere Avenue, Baltimore, Maryland 21215. E-mail: pgurbel@lifebridgehealth.org.

REFERENCES

1. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908-13.
2. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171-5.
3. Samara WM, Bliden KP, Tantry US, Gurbel PA. The difference between clopidogrel responsiveness and posttreatment platelet reactivity. *Thromb Res* 2005;115:89-94.
4. Bonello L, Tantry US, Marcucci R, et al., for the Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol* 2010;56:919-33.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122.
6. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
7. Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Michelson AD. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 2007;50:1822-34.
8. Sibbing D, Steinhubl SR, Schulz S, Schömig A, Kastrati A. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. *J Am Coll Cardiol* 2010;56:317-8.
9. Mangiacapra F, Patti G, Barbato E, et al. A therapeutic window for platelet reactivity for patients undergoing elective percutaneous coronary intervention: results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity for Outcome Validation Effort) study. *J Am Coll Cardiol Intv* 2012;5:281-9.
10. Mangiacapra F, Patti G, Peace A, et al. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. *Am J Cardiol* 2010;106:619-23.
11. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet Therapy for Reduction of MYocardial Damage During Angioplasty-Platelet Reactivity Predicts Outcome) study. *J Am Coll Cardiol* 2008;52:1128-33.
12. Patti G, Pasceri V, Vizzi V, Ricottini E, Di Sciascio G. Usefulness of platelet response to clopidogrel by point-of-care testing to predict bleeding outcomes in patients undergoing percutaneous coronary intervention (from the Antiplatelet Therapy for Reduction of MYocardial Damage During Angioplasty-Bleeding study). *Am J Cardiol* 2011;107:995-1000.
13. Brar SS, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011;58:1945-54.
14. Stone GW. Assessment of dual antiplatelet Therapy with Drug-Eluting Stents A Large-Scale, prospective, multicenter Registry Examining the Relationship between platelet responsiveness and Stent thrombosis after DES implantation. Presented at: Transcatheter Cardiovascular Therapeutics Meetings 2011; San Francisco, CA.
15. Price MJ. The GRAVITAS (Gauging Responsiveness with A Verify-Now assay-Impact on Thrombosis And Safety) trial (abstr). Presented at: American Heart Association 2010 Scientific Sessions 2010, Chicago, IL.
16. Campo G, Parrinello G, Ferraresi P, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. *J Am Coll Cardiol* 2011;57:2474-83.
17. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
18. Trenk D. Primary results of Testing platelet Reactivity in patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel TRIGGER-PCI study. Presented at: Transcatheter Cardiovascular Therapeutics Meetings 2011; San Francisco, CA.

Key Words: adenosine diphosphate (ADP) ■ percutaneous coronary intervention (PCI) ■ platelet reactivity.